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II.4.8 Treatment of Gender Dysphoria

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Summary

Hormonal sex reassignment of transsexuals aims to reduce the hormonally induced secondary sex characteristics of the original sex and to induce the secondary sex characteristics of the new sex.

- In male-to-female transsexuals a complete reduction of androgen action favours feminizing effects of oestrogens. The risk of venous thrombosis is high with ethinyloestradiol but much lower with transdermal or oral 17β-oestradiol. Development of prolactinomas has been observed, usually with an overdose of oestrogens. Breast cancer, though infrequent, remains a risk.
- Female-to-male transsexuals receive high-dose testosterone treatment. If menstrual periods are not suppressed a progestin may be added. Side-effects are acceptable but extirpation of ovaries and internal genitalia in due course is recommended as a safeguard against malignant development.
- Transsexualism is increasingly diagnosed in juveniles. Hormonal treatment to delay pubertal development of their original sex may be an option.

Transsexualism is the condition in which a person with apparently normal somatic sexual differentiation of one gender is convinced that he or she is actually a member of the opposite gender. It is associated with an irresistible urge to be that gender hormonally, anatomically and psychosocially.

In 2004, the international organization involved with professional help to transsexuals, the Harry Benjamin International Gender Dysphoria Association, drafted Standards of Care (SOC) available at http://www.hbigda.org. The major purpose of the SOC is to articulate this organization's professional consensus about the psychological, medical and surgical management of gender identity disorders. These standards provide guidance to professionals practising in this area, who often work in isolation from mainstream medicine. It may also be of help in legal medicine to identify professional standards. Persons with gender identity disorders, their families and social institutions may use the SOC as a means to understand the current thinking of professionals.

Before initiating hormonal or surgical treatment that will change a person's gender, the physician should counsel the patient about realistic expectations from treatment. The only benefit sex reassignment can bring is relief of gender dysphoria; all human problems outside the area of gender dysphoria will remain. Unrealistic expectations that subjects may have of the success of hormonal and surgical treatment for their transition to the desired sex must be addressed. Contacts with other transsexuals who are already in the process of changing over to the new sex or who have completed this process may be helpful in shaping a subject's expectations of what can be achieved and what problems, personally and socially, may arise in the transition to the new sex.

II.4.8.1 Real Life Test

When hormone treatment starts, or maybe even earlier, the "real life test" should begin. It is an extended period of full-time living as a member of the desired sex. The "real life test" allows the subject and the attending professional to monitor the experience in the new sex status as he/she habituates his/her responses to other people. Without this test of how others react and how he/she reacts to others, the subject knows only his/her private convictions and fantasies of being a member of the opposite sex. Convictions and fantasies may be unrealistic and may lead to magical expectations of life in the new sex.

Embarking on the "real life test" may be done in a stepwise fashion; for instance, first in a trusted environment and later in public. The subject should have lived at least one full year full-time in the new sex before irreversible surgical reassignment is considered.

The "real life test" may be prolonged if too many hurdles present themselves during the test period. During the "real life test" the subject should stay in contact with a mental health professional to allow assessment of the success of the test and to discuss how to overcome problems that almost inevitably arise during this period.

II.4.8.2 Hormonal Sex Reassignment

Hormonal reassignment has two aims (Levy et al. 2003):

- To reduce the hormonally induced secondary sex characteristics of the original sex as much as possible, though complete elimination is rare. As an example, in male-to-female transsexuals, the previous effects of androgens on the skeleton, such as the greater height of men than women, the size and shape of hands, feet, jaws and pelvis, cannot be reversed. Conversely, the relatively lower height and the broader hip configuration of female-to-male transsexuals compared to men will not change with androgen treatment.
- To induce the secondary sex characteristics of the new sex.

II.4.8.2.1 Male-to-Female

To male-to-female transsexuals, elimination of sexual hair growth, induction of breast formation and a more female fat distribution are essential. To accomplish this, a near-complete reduction of the biological effects of androgens is required. Administration of oestrogens alone will suppress gonadotrophin output and therefore androgen production, but dual therapy with one compound that suppresses androgen secretion or action and a second compound that supplies oestrogen is more effective.

Suppression of Androgen Secretion or Action

Several agents are available to inhibit androgen secretion or action. In Europe, the most widely used drug is cyproterone acetate (usually 50 mg twice daily), a progestational compound with antiandrogenic properties. If it is not available, medroxyprogesterone acetate, 5–10 mg/day, is an alternative, although less effective. Nonsteroidal antiandrogens, such as flutamide and nilutamide, are also used, but they increase gonadotrophin secretion, causing increased secretion of testosterone and oestradiol; the latter is a desirable effect in this context. Spironolactone (100 mg twice daily), a diuretic with antiandrogenic properties, has similar effects. Long-acting gonadotrophin-releasing hormone (GnRH) agonists, used as monthly injections, also inhibit gonadotrophin secretion. Finasteride (5 mg/day), a 5-α-reductase inhibitor, might also be considered.

Oestrogen

There is a wide range of oestrogens from which to choose. Oral ethinyloestradiol (50–100 μg/day) is a potent and inexpensive oestrogen, but it may cause venous thrombosis, particularly in subjects over 40 years (van Kesteren et al. 1997; Moore et al. 2003; Toorians et al. 2003) and should no longer be used. Oral 17β-oestradiol valerate 2–4 mg per day or transdermal 17β-oestradiol, 100 μg twice a week, is the treatment of choice (Toorians et al. 2003).

Consequences

There are a variety of consequences of hormonal therapy in male-to-female transsexuals:

- Sexual hair – adult male beard growth is very resistant to inhibition by combined hormonal intervention, and in Caucasian subjects additional measures to eliminate facial hair are necessary. Sexual hair growth on other parts of the body respond more favourably (Giltay and Gooren 2000).
- Breast development – breast formation starts almost immediately after initiation of oestrogen administration and goes through periods of growth and standstill. Androgens have an inhibitory effect on breast formation and, therefore, oestrogens will be most effective in a milieu devoid of androgen action. After 2 years of oestrogen administration, no further development can be expected. It is quantitatively satisfactory in 40–50% of the subjects. The attained size is often disproportional to the male dimension of the chest and height of the subject, so the subject may desire surgical breast augmentation. Older age also impedes full breast formation.
- Skin – androgen deprivation leads to a decreased activity of the sebaceous glands, which may result in a dry skin or brittle nails (Giltay and Gooren 2000).
- Body composition – following androgen deprivation there is an increase in subcutaneous fat and a decrease in lean body mass. Body weight usually increases.
- Testes – lacking gonadotrophic stimulation, the testes become atrophic and may enter the inguinal canal, which may cause discomfort.
- Prostate – atrophy of the prostate may produce transient dribbling following micturition. This is usually temporary.

- Voice – antiandrogens and oestrogens have no effect on the properties of the voice, so male-to-female transsexuals may wish to consult a specialized phoniatric centre for speech therapy. Maleness of the voice is not so much determined by the pitch of the voice as by chest resonance and volume. Speech therapy may lead to more feminine speech (de Bruin et al. 2000). Laryngeal surgery may change the pitch of the voice but reduces its range.

Long-term Therapy

After reassignment surgery, including orchiectomy, hormone therapy must be continued. Some subjects still experience growth of sexual hair in a male pattern, and antiandrogens appear to be effective in reducing it, although the dose may be reduced. Continuous oestrogen therapy is required to avoid symptoms of hormone deprivation and, most importantly, to prevent osteoporosis (van Kesteren et al. 1998). We have found that oestrogens alone are capable of maintaining bone mass in male-to-female transsexuals. There was an inverse relationship between serum luteinizing hormone (LH) concentrations and bone mineral density, so serum LH may serve as an indicator of the adequacy of sex steroid administration.

II.4.8.2.2 Female-to-Male

The goal of treatment in female-to-male transsexuals is to induce virilization, including a male pattern of sexual hair and male physical contours, and to stop menses. The principal hormonal treatment is a testosterone preparation. The most commonly used preparations are testosterone esters in doses of 200–250 mg intramuscularly every 2 weeks. Recently, transdermal testosterone gels have become available. Occasionally menstrual bleeding does not cease with this regimen, and addition of a progestational agent is necessary. If a transdermal testosterone preparation is used, addition of a progestational agent is nearly always necessary.

Consequences

There are a variety of consequences of hormonal therapy in female-to-male transsexuals:

- Hair – the development of sexual hair follows essentially the pattern observed in pubertal boys: first the upper lip, then chin, then cheeks, etc. (Giltay and Gooren 2000). The degree of hirsutism can usually be predicted from the degree and pattern in male members of the same family. The same applies to the occurrence of alopecia androgenica.
- Voice – deepening of the voice occurs after 6–10 weeks of androgen administration and is irreversible. Androgen administration leads to a reduction of subcutaneous fat but increases abdominal fat. The increase in lean body mass is on average 4 kg, and the increase in body weight is usually greater.
- Acne – acne occurs in approximately 40 %, usually very pronounced on the back, similar to that observed in hypogonadal men starting androgen treatment past the age of normal puberty (Giltay and Gooren 2000).
- Clitoral enlargement – clitoral enlargement occurs in all, but the degree varies. In approximately 5–8 %, the size becomes sufficient for vaginal intercourse.
- Libido – most subjects will note an increase.
- Other – ovaries show polycystic changes, and androgen administration may decrease glandular activity of the breasts but does not reduce their size.

After bilateral oophorectomy, androgen therapy must be continued to maintain virilization and prevent osteoporosis (van Kesteren et al. 1998). Suppression of the serum LH concentration to within the normal range can be used to indicate the adequacy of androgen administration.

II.4.8.3 Side-Effects of Hormonal Sex Reassignment

In a review of 816 male-to-female transsexuals and 293 female-to-male transsexuals (total exposure 10,152 patient years), mortality was no higher than in a comparison group (van Kesteren et al. 1997). However, cross-sex hormone administration may be associated with side-effects (Futterweit 1998):

- Venous thromboembolism – the incidence of these side-effects was 2–6 % in male-to-female transsexuals treated with oral ethinyloestradiol. In vitro studies show that this thrombogenic effect is typical of oral ethinyloestradiol but not of oral 17β-oestradiol (Toorians et al. 2003). Because immobilization is also a risk factor for venous thromboembolic events, oestrogen administration should be discontinued 3–4 weeks before elective surgical interventions. Once subjects are fully mobilized again, oestrogen therapy may be resumed.
- Atherosclerosis – although the considerable sex difference in the prevalence of cardiovascular disease between men and women would lead one to expect an effect of hormonal treatment, the actual risk remains to be established. The effects of

oestrogen administration to male-to-female and of androgens to female-to-male transsexuals on biochemical risk markers have been studied. It appeared that oestrogen administration had more negative effects on these risk markers than androgens (Elbers et al. 2003).

- Lactotroph adenoma – four cases of lactotroph adenoma (prolactinoma) following high-dose oestrogen administration have been reported in subjects who had normal serum prolactin concentrations before therapy (van Kesteren et al. 1997). Though causality has not been established, we recommend that serum prolactin levels continue to be monitored in oestrogen-treated male-to-female transsexuals, also in the long-term.
- Breast cancer – there are two reports of male-to-female transsexuals who were found to have breast carcinomas while they were receiving oestrogen treatment (van Kesteren et al. 1997). In recent years no cases have been observed, but self examination of the breast must be part of the monitoring of oestrogen administration, following the same guidelines that exist for other women.
- Prostate cancer – three cases of prostate cancer in male-to-female transsexuals taking oestrogen have been reported (Van Haarst et al. 1998). It is not clear whether these cancers were oestrogen-sensitive or whether they were present before oestrogen administration started and progressed to become hormone-independent.
- Ovarian cancer – we recently observed two cases of ovarian carcinoma in a long-term, testosterone-treated, female-to-male transsexual. Ovaries of female-to-male transsexuals taking androgens show similarities with polycystic ovaries, which are also more likely to develop malignancies. Therefore, it seems reasonable to remove the ovaries of androgen-treated female-to-male transsexuals after a successful transition to the male role.
- Contraindications – because of the potential side-effects described above, hormonal treatment is contraindicated in certain situations. Contraindications to oestrogen use are a strong family history of breast cancer or a lactotroph adenoma, and to androgen-use lipid disorders with cardiovascular complications. Contraindications against the use of high doses of either sex steroid are cardiovascular disease, cerebrovascular disease, thromboembolic disease, marked obesity, poorly controlled diabetes mellitus, and active liver disease (Futterweit 1998; Levy et al. 2003; Moore et al. 2003).

II.4.8.4 Juvenile Gender Dysphoria

Adult transsexuals often recall that their gender dysphoria started early in life, well before puberty. Children with gender identity problems increasingly come to the attention of the psychomedical care system. A reliable estimation indicates that only about 20% will become transsexuals in adolescence (Cohen-Kettenis and van Goozen 1998). Homosexuality will be more often the outcome.

If, in expert opinion, a child's cross-sex gender identity will not change during long-term follow-up the individual may be spared the torment of (full) pubescent development of the "wrong" secondary sex characteristics (Cohen-Kettenis and van Goozen 1998). Depot forms of luteinizing hormone releasing hormone (LHRH) antagonists/agonists, following the regimen in children with precocious puberty, can be used when clear signs of sexual maturation are evident in order to delay pubertal development until an age that a balanced and responsible decision can be made to transition to the other sex (Gooren and Dellemarre van de Waal 1996).

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II.4.9 Treatment of Sexual Dysfunction

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Summary

The introduction of the phosphodiesterase type 5 inhibitors (PDE inhibitors) has been a major step forward in the treatment of erectile dysfunction (ED). Though efficacious and safe, 50% of men discontinue treatment, largely because other sexological issues have not been properly addressed. To predict onset and duration of action, insight into the pharmacokinetics of the PDE inhibitors is required.

- In men whose testosterone levels are low, testosterone substitution may booster the efficacy of PDE inhibitors.
- Before receiving PDE inhibitor the cardiovascular status of a patient must be assessed.

The main action of testosterone is on the central nervous system. It improves libido and mood. Levels in the low-normal range suffice.

Hyperprolactinaemia impairs sexual interest and leads to secondary ED. Dopamine agonists are the treatment of choice.

Men with paraphilias may be treated with drugs that lower androgen action if the desire to act out their paraphilia is high.

II.4.9.1 Erectile Dysfunction

The availability of a highly efficacious and relatively safe compound such as the phosphodiesterase type 5 inhibitor sildenafil has had a profound impact on diagnosis and treatment of erectile dysfunction (ED). Once the domain of the urologist attempting to define the precise aetiology, ED is now largely treated by first-line physicians, without much of a diagnostic work-up. Despite the simplicity and safety of the present therapy of ED, approximately 50% of patients discontinue treatment. The reasons for discontinuations lie mostly in an incomplete evaluation of the sexual problem. Hypogonadism, ejaculatory dysfunction, lower urinary tract symptoms, depression, and last but not least partner issues may all be components of the sexual dysfunction of the patient, and apparently restoration of erectile function does not necessarily imply restoration of a happy sex life (Montorsi and Althof 2004). Nevertheless, the introduction of the phosphodiesterase type 5 inhibitors has substantially improved the therapeutic options for ED.

II.4.9.1.1 Phosphodiesterase Type 5 Inhibitors

The identification of pathways in the physiology of erection and the discovery of the importance of nitric oxide (NO) and its downstream effects lie at the basis of the development of the phosphodiesterase type 5 inhibitors (PDE inhibitors). Subsequent to sexual stimulation, NO arising from the nerve endings of non-adrenergic non-cholinergic innervation of the corpus cavernosum activates guanylyl cyclase, an enzyme that catalyses the conversion of GTP to cGMP. At the cellular level cGMP is broken down to 5-GMP by phosphodiesterase type 5. Via a molecular cascade cGMP lowers intracellular calcium and vascular smooth muscle of the corpus cavernosum relaxes, resulting in an increased penile blood flow thus facilitating the initiation and maintenance of an erection.

The pharmacological action of PDE inhibitors manifests itself only when a person is sexually aroused, which distinguishes this class of drugs from intracavernosal injections. This is also important information for the user (Seftel 2004).

The efficacy and relative safety of PDE inhibitors is well documented now. They have a common mode of action, the inhibition of PDE 5. Selectivity and tissue localization of the PDE inhibitors determine the side-effect profiles and safety.

There are presently three PDE inhibitors available for prescription: sildenafil, vardenafil and tadalafil. All are efficacious, but there are differences in pharmacokinetic profile, interactions with food and drugs, and possible side-effects. Taking nitrate medications is an absolute contraindication to the use of PDE inhibitors since PDE inhibitors increase the potential for excessively low blood pressure. Low blood pressure, though to a lesser degree, has also been observed with PDE inhibitors in men taking alpha adrenoreceptor antagonists, such as doxazosin, prazosin, terazosin, alfuzosin